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16th June, 1958.

Prof. Joshua Lederberg,
Walter & Eliza Hall Institute of Medical Research,
MELBOURNE,
Australia.

Dear Prof. Lederberg,

I was fascinated by your letter in Nature of May 17th, both by the techniques and the interpretation. I am not a microbiologist nor a serologist, but as a geneticist I have tried to follow your work. The idea of production of antibody being limited to one kind per cell reminds me of some work of Beale's in Paramecium. As I remember it was antigen production which was limited to one at a time of a number of alternatives, the specific antigen varying with temperature.

However, the novelty of the phenomenon you describe, behoves us to search widely for possible explanations. It is for this reason that I am emboldened to suggest two alternative explanations which come to mind.

1). All cells producing antibody produce both kinds but the specific groups are attached to a non-specific "antibody organelle" which might however be a generic "Salmonella antibody". This organelle is used up by 10 bacteria of one species so that it is no longer available for the second species, the antibodies for which have been smothered by the antigens of the first.

2). The second hypothesis has been suggested to me by my colleague Muldal. The maximum amount of antibody per cell is finite and less than equivalent to the antigens of 20 bacteria. Production of the two antibodies is independent so that only a small minority of the cells will produce all of one kind. The rest will produce a mixture, but such a mixture will not be sufficient to deal with the antigens of 10 bacteria of one kind. Such cells would be excluded from your analysis because "If even one organism in the droplet remained motile, this was recorded as 'no inhibition' ".

Both hypothesis are open to testing.

1). By using fewer bacteria per droplet - say 3. This would increase the proportion with complete inhibition. But if the hypothesis is correct some of these should have enough antibody organelle left to immobilize a further 3 bacteria of the second species.

P.T.O.

2). Use 10 bacteria but test all single cells which immobilize some of the first species with 10 of the second species. These should contain varying amounts of the second antibody, according to the total antibody production per cell.

I hope you will feel that this letter has been constructive.

Yours sincerely,

A.J.Bateman.

P.S. I have just noticed an anomaly in your data. Should not one expect the proportion of inhibitory droplets to increase exponentially with the number of cells in the drops? $(1-e^{-kn})$ where n is the number of cells in the drops and, for the data presented in Table 1, $k = ca\ 0{\cdot}15$. If k were small the proportion of inhibitory drops would increase linearly with number of cells in the drops. The actual increase appears to be much slower than expected.

AJB.